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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,483	09/17/2001	Christian Siebel	RMES-02	6505

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/954,483	SIEBEL ET AL	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-26 & 29-31) in Paper No. 16, filed 6/2/03 is acknowledged. Claims 27-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers, no computer readable format (CRF) was filed, no paper sequence was filed and no attorney statement was filed. **This specifically refers to the sequence shown in Figure 14, which does not have a corresponding sequence in the sequence listing (e.g. compare the last 20 nucleotides in Figure 14 with the sequences in the sequence listing).** If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP § 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of the claims features a targeting construct comprising a positive selection marker, two regions of homology to a target sequence and a "regulator" that controls expression of the positive selection marker. The specification describes the regulator as being "...a sequence or sequences (i.e. polynucleotide sequence or protein sequence) that regulates or controls expression of the selectable marker..." (page 8, lines 15-18). The specification also teaches that the regulator functions to down regulate expression of the selectable marker on the targeting construct when the construct is randomly incorporated into the target genome by illegitimate recombination events (e.g. pages 5-6, bridging paragraphs). This allows the skilled artisan to select for the presence of the positive selection marker and reduce the number of false-positives for proper incorporation of the targeting construct into the target sequence due to the reduced expression of the marker in those cells where the marker is randomly incorporated. Due to this feature, the skilled artisan does not need to utilize negative selection methodologies. The rejected claims encompass an enormous genus of targeting constructs comprising a "regulator" comprising literally any protein or DNA sequence, or combination thereof, arranged in any fashion on the targeting construct. The "regulator" must function, however, to down regulate

expression of the positive selection marker if the targeting construct does not insert into the target sequence.

The specification describes a single relevant working example where the two sequences with homology to the target sequence flank a selectable marker cassette and where a gene encoding a transcriptional repressor (lacI) is located on the construct on the other side of one of the two targeting sequences from the positive selection marker (e.g. neo^r). The gene encoding the selectable marker in this case is under the control of a promoter comprising the cognate operator sequence (lacO) for the repressor such that, if random incorporation of the entire targeting construct into the host genome occurs, expression of the positive selection marker is repressed. A double crossover event between the targeting sequences on the construct and the target sequence in the genome, however, results in the release of at least part of the "regulator" and allows more efficient expression of the selectable marker. No other arrangement of the different components of the targeting constructs is described in the instant specification. For example, no description is provided for an alternate arrangement of the two regions of homology to the target sequence and the positive selection marker. The specification asserts that a transcriptional silencer element (e.g. NRF, COL4, etc.) could also work in *cis* to accomplish the same effect, but no arrangement of such an element has been described in the instant specification. Thus, the instant specification does not provide a basis for one of skill in the art to envision a sufficient number of other arrangements of the recited elements to describe the broadly claimed targeting vectors embraced by the rejected claims.

The prior art does not appear to teach a system of utilizing a "regulator" to down regulate expression of a positive selection marker in targeting constructs when the constructs are

randomly inserted into the genome of a host cell. Therefore, the prior art does not offset the deficiencies of the instant specification concerning a basis for one to envision a number of alternative arrangements of the recited elements or other types of regulators sufficient to describe the broadly claimed genus.

Given that the term "regulator" apparently encompasses a huge number of possible DNA sequences and proteins sequences, or combinations thereof, and given the functional limitations of what the "regulator" must accomplish, the skilled artisan would not be able to envision a sufficient number of embodiments of the claimed invention to describe the broadly claimed genus of targeting vectors. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the claimed invention at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of the claims recites a limitation of a "regulator". The metes and bounds of this term are unclear in the context of the claimed invention. The specification describes the regulator as being "...a sequence or sequences (i.e. polynucleotide sequence or protein sequence) that regulates or controls expression of the selectable marker..." (page 8, lines 15-18). The specification also teaches that the regulator functions to down regulate expression of the selectable marker on the targeting construct when the construct is randomly incorporated into the

target genome by illegitimate recombination events (e.g. pages 5-6, bridging paragraphs). It is unclear how a regulator can be comprised within a targeting vector and also be a protein Also, it is unclear whether the term necessarily refers to protein and nucleic acid sequences in certain embodiments. For example, in the embodiment exemplified in the instant specification (e.g. in Figure 5), the targeting vector comprises an operator sequence (lacO) operatively linked to the promoter that drives the selectable marker, as well as a sequence encoding the lac repressor (lacI). In this case, does the term "regulator" refer to the cis-acting lacO sequence, the coding sequence for lacI or the repressor protein; or does it necessarily refer to a combination of all three? It would be remedial to amend the claim language to make clear which elements, protein or DNA sequence or both, must be present in order for a targeting construct to satisfy the limitation of comprising a "regulator".

Claim 20 is vague and indefinite in that it recites "introducing a targeting vector" without specifying into what or to whom the vector is introduced.

Claims 20 and 22 are vague and indefinite in that they recite the limitation of a sequence that is "substantially" homologous to another nucleic acid. This term is not explicitly defined in the specification and is inherently indefinite. It is unclear, for example, how "substantially homologous" nucleic acids would differ from "homologous" nucleic acids in terms of the instant invention. It would be remedial to simply delete this term from the claims as it does not appear to add anything to the claim.

Claim 22 is vague and indefinite in that it recites "inserting a targeting vector" without specifying into what the vector is inserted.

Claims 24 is vague and indefinite in that it is improperly dependent upon itself. This affects claims 23 and 25 which are dependent upon claim 24.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi et al (AC; U.S. Patent No. 5,627,059; see the entire patent).

Claim 26 is drawn to an isolated host cell comprising a modification or disruption of a target gene, wherein the target gene is modified or disrupted by insertion of a targeting vector into the host cell.

Capecchi et al teach the use of positive-negative targeting vectors that comprise targeting sequences flanking a positive selection marker and which further comprise a negative selection marker outside of the targeting cassette that allows for selection against random insertion events (e.g. Abstract; Figure 1). The '059 patent teaches examples where particular genes in a target cell have been inactivated by insertion of a targeting construct (e.g. Example 4-Disruption of the hox1.4 locus in mouse ES cells).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Examiner
Art Unit 1636

Ggl
August 8, 2003